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HEMOLYTIC STREPTOCOCCI OF THE APPENDIX VERMIFORMIS

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The significance of hemolytic streptococci in the etiology of appendicitis is not well known. Osler¹ says that the *Streptococcus pyogenes* is present in a large number of cases. Rose and Carless² appear to agree with Osler in this respect. Rosenow and Dunlap³ reported an epidemic of streptococcus appendicitis at Camp Culver, and according to their report the cause was a hemolytic streptococcus. Takaki⁴ and Ungerman⁵ reported the isolation of *Streptococcus pyogenes* from the vermiform appendix. Others have reported the occurrence of appendicitis due to streptococci, but it is not clear whether the organisms were hemolytic or nonhemolytic. In view of the foregoing facts, I undertook an investigation of this lesion with the object of determining the frequency with which hemolytic streptococci are found in the normal appendix and in acute and chronic appendicitis and, if possible, the rôle they play as a primary etiologic factor in appendicitis.

TECHNIC

In all, 175 appendixes were examined; the first 50 were used in a preliminary way in order to develop the technic. The appendixes were gathered from various clinics and I am indebted to Dr. Meyer and Dr. Stangl of Cook County Hospital, Chicago; Dr. Ochsner and Dr. Nuzum of Augustana Hospital, Chicago; and to others for material used. Immediately after removal and while still free from external contamination, the appendix was placed in sterile cheese cloth several layers thick, the whole wrapped in clean waxed paper and placed in the icebox. No appendix was used that had been in the icebox more than 24-36 hours; the gross examination, smears of contents and of the mucosa, and bacterial cultures of the mucosa and wall were made as soon as possible. The instruments used in dissecting the material, which was done on a sterile porcelain plate, were thoroughly sterilized before used. Cultures of the mucosa and wall were made by scraping the mucosa and muscular layers with a sterile knife, and using some of the finely divided tissue

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¹ Principles and Practice of Medicine, 1918.

² Manual of Surgery, 1919.

³ Jour. Infect. Dis., 1916, 18, p. 383.

⁴ Sei-i-Kwai, Med. Jour., 1915, 34, p. 21.

⁵ Centralbl. f. Bakterirol., 1909, 50, p. 513.

for broth and poured blood-agar plates. The plates and broth cultures were incubated for 24 hours at 37 C. and the colonies and growth in broth were then examined by methylene blue and Gram's stains. The plates were examined with special reference to hemolysis, and to the size, shape, color, elevation, pigmentation, moisture, predominance, and variety of any colonies present. Only those colonies that gave a distinct hemolysis about a small pinpoint grayish slightly elevated growth, and that on staining showed gram-positive cocci growing in chains or as diplococci, were tabulated as hemolytic streptococci. Although these tests are practically conclusive, later tests were also made and the organisms grouped in accordance with Holman's⁶ scheme. All nonhemolytic streptococci producing a green halo were classed tentatively as *Streptococcus viridans* without further attempt at classification. After cultures and smears had been made, the specimen was again placed in the icebox so as to be available for reexamination should uncertain results appear.

In this series, 48 were normal and 77 pathologic. The criteria for this differentiation will be discussed later. Two strains of hemolytic streptococci were isolated from the 48 apparently normal appendixes; these were strains 18 and 54 and belong to the type *Streptococcus infrequens* (Holman). Four strains of hemolytic streptococci were found in the 77 pathologic appendixes, namely, strains 37, 39, 71 and 104, all belonging to the type *Streptococcus infrequens*, except strain 104, which belonged to the type *Streptococcus hemolyticus* II. From this it appears that hemolytic streptococci occurred in this series in normal appendixes in 4.17 % and in the pathologic in 5.2 %. No hemolytic streptococci were isolated from 25 appendixes presenting evidence of chronic inflammation. The instances of acute appendicitis yielding hemolytic streptococci presented either ulcerative or gangrenous appendixes.

Other findings were: 108 strains of nonhemolytic colon bacilli, of which 45 strains were found in 48 normal appendixes and 63 strains in 77 pathologic appendixes; 51 strains of hemolytic colon bacillus, of which 19 were found in 48 normal appendixes; 32 strains of *Streptococcus viridans* were isolated from 48 normal appendixes. Two probable pneumococcus strains, one case of pinworm and many large unidentified bacilli, which were, no doubt, nonpathogenic, were the other results.

In the normal appendix, hemolytic streptococci, when found, occurred only in small numbers. One loopful of the macerated mucosa and wall when added to blood agar, plated and incubated for 24 hours gave 6 to 10 colonies. Streptococci in chains of 4 to 12 were found

⁶ Jour. Med. Res., 1916, 34, p. 377.

in smears from the walls and contents, but these no doubt were practically all viridans as indicated by the blood-agar plates. Leukocytes were seen only occasionally in the normal appendix. Hemolytic streptococci when isolated from pathologic appendixes were present in large numbers; furthermore, they were in almost pure culture. One loopful of the contents or macerated walls of the appendix when placed in 5 c c of blood agar, plated and incubated for 24 hours gave innumerable typical hemolytic colonies. The third dilution was usually necessary for the isolation of individual colonies. Smears from the contents and walls showed an almost pure culture of streptococci, which were gram-positive and in chains of 4 to 15. One case gave practically a pure culture of diplococci, which on growth in beef broth developed chains of 6 to 18. The smears, furthermore, showed an enormous amount of polymorphonuclear leukocytic infiltration; many pus cells and cells with ingested bacteria were present. Blood cells were present, too, but most of these were already disintegrated.

The hemolytic streptococci in this series were pathogenic for rabbits. The strains were incubated in 5 c c of plain beef broth at 37 C. for 18 to 24 hours; 3 c c were injected intravenously into the lateral vein of the ear of young healthy rabbits weighing 1,000 to 1,200 gm. Two rabbits were similarly injected with the sterile beef broth for controls. Strains 37, 39, 71 and 104 killed the rabbits in 48 to 72 hours. The organisms were recovered in pure cultures from the heart blood, 10 drops of the blood when plated giving 20 to 30 colonies. Strains 18 and 54 killed rabbits in 5 days when similarly injected. The organism was recovered from the grayish pus in the joints. No other gross lesions were noted.

As stated, of the 125 appendixes of which a record was kept, 77 were pathologic and 48 normal. This classification was made on the basis of gross appearances and clinical diagnosis. It is to be emphasized that at times it becomes extremely difficult to determine whether an appendix is normal or slightly pathologic. The statement has been made by pathologists and surgeons that in adults an absolutely normal appendix does not exist.

A word should be said in regard to the possible avenues by which hemolytic streptococci reach the appendix. As elsewhere, three routes are usually considered: contiguity, progression and hematogenous or lymphogenous channels. There was no periappendiceal involvement in any case in which the hemolytic streptococcus was found, and for

that reason, one may, with reasonable certainty, say that the mode of entrance was either by progression along the gastro-intestinal tract or hematogenous. Rosenow⁷ and others⁸ have laid stress on the hematogenous route, and name as the primary source the tonsils in a majority of the cases. Rosenow produced appendicitis experimentally by intravenous injection of streptococci and colon bacilli. A number of investigators have emphasized the selective action of certain bacteria for the appendix.

Hemolytic streptococci, as a rule, do not frequent the gastro-intestinal tract. The countless numbers of these bacteria that pass down the esophagus encounter their fate in the stomach because the ferments and acid there show a decided antagonistic action toward them. They may, however, enter the intestinal tract in a lump or mass of food. An achylia may permit them to pass into the bowel where a more favorable medium is afforded, although not the optimum. Davis¹⁰ fed hemolytic streptococci to rabbits every day for a month and only occasionally recovered them in the stools. Holman¹¹ isolated 4 strains from feces; Oppenheim 5 strains from 15 stools;¹² and Broadhurst¹³ 9 from 31 stools. This is of interest here because 5 out of the 6 strains isolated by me from normal and pathologic appendixes were of the same type.

In 1890 Kruse and Pasquale¹⁴ found streptococci in large numbers in feces of patients with acute dysentery. They were probably non-hemolytic. Beck,¹⁵ in 1892, isolated a streptococcus from the stools of cholera nostras and concluded that this organism was the causative agent, but he does not state whether the organism isolated by him was hemolytic or nonhemolytic. Lameris and Harreveld¹⁶ obtained streptococci from stools of patients suffering from diarrhea following the use of contaminated milk, but they were not pathogenic for animals.

SUMMARY AND CONCLUSIONS

Hemolytic streptococci were found in two of 48 normal appendixes (4.17 %) and in 4 of 77 pathologic appendixes (5.2 %).

⁷ Jour. Infect. Dis., 1915, 16, p. 240.

⁸ McCoy, Lancet-Clin., 1916, 116, p. 49.

⁹ Pilot and Davis, Jour. Infect. Dis., 1919, 24, p. 386.

¹⁰ Davis, Jour. Am. Med. Assn., 1919, 72, p. 323.

¹¹ Jour. Am. Med. Assn., 1919, 72, p. 319.

¹² Jour. Med. Res., 1916, 34, p. 377.

¹³ Jour. Infect. Dis., 1920, 26, p. 117.

¹⁴ Jour. Infect. Dis., 1915, 17, p. 277; Ztschr. f. Hyg. u. Infektionskr., 1893, 16, p. 1.

¹⁵ Centralbl. f. Bakteriologie, 1892, 12, p. 632.

¹⁶ Ztschr. f. Fleisch. u. Milch Hyg., 1901, 11, p. 114.

In the pathologic series they were found in acute cases only. They were not recovered from the chronically inflamed appendixes.

When hemolytic streptococci occurred in pathologic appendixes they were present in large numbers and in practically pure culture; while when found in the normal appendixes they were few in number.

Two types were found, namely, *Streptococcus infrequens* (5 strains) and *Streptococcus hemolyticus* II (1 strain).

Hemolytic streptococci apparently do not play an important rôle in the production of appendicitis; however, when they occur in the pathologic appendix, they usually predominate and appear to be the principal etiologic agent.